REMARKS

Summary of Amendments

Claim 4 has been amended to add the modifier "endless" before "recirculation-path system," in the recitation of the fifth element in the claim, and to add the modifier "circuit-" before "feed," to clarify that the claimed pump circuit-feeds the reaction mixture through the (endless) recirculation-path system. Both amendments are supported by the specification as filed—for example, in paragraphs [0009] and [0023] for the recitation "endless," and in paragraphs [0012] and [0023] for the recitation "circuit-feeds."

Claims 5, 6, 8 and 13-17 were canceled in Applicant's June 9, 2006 reply to the previous Office action.

Claims 4, 6, 7, and 9-12 remain pending.

Claim Rejections – 35 U.S.C. § 103

1. Claims 4, 6, 7 and 9-12; combined disclosures in Haff et al. '413

Claims 4, 6, 7 and 9-12 remain rejected as being unpatentable over a combination of embodiments disclosed in European Pat. App. Pub. No. 0 636 413 A2.

Applicant and Applicant's counsel greatly appreciate the Examiner's careful and detailed reexamination of the merits of the present application, and attentive, considerate response to Applicant's previous reply.

Page 4 of the Office action admits

> Haff et al. does not expressly disclose that the *same* reaction mixture is cycled through the temperature zones of the apparatus in Figure 1; however, Haff et al. does disclose one amplification reaction mixture cycled through different temperature zones multiple times in Figure 2.
>
> It would have been *prima facie obvious* to a practitioner of ordinary skill in the art at the time of invention to . . . flow the same reaction mixture through the apparatus of Figure 1 multiple times, since Haff suggests such a modification to continuously amplify the same reaction mixture through multiple amplification cycles.

(Emphasis is in original.)

Fig. 2 of Haff et al. illustrates a process of *reciprocating*, not recirculating, reaction mixture through "a length of capillary tubing 50 that is routed in and out of

hot and cold sources of the appropriate temperature a number of times" (column 13, lines 6-9).

That is, the embodiment represented in Fig. 2 of Haff et al. is *prima facie* a system for delivering a reaction mixture *one time* from a syringe 51, reciprocating the mixture through a one-pass course that zigzags between two different temperature baths, and emptying finished PCR product into a collection container 56. With regard to this embodiment, nowhere does Haff et al. disclose, teach, or suggest recirculating the PCR product in the container back into the syringe 51.

As recited in claim 4, a DNA continuous amplification apparatus according to the present invention *recirculates* the reaction mixture, by in contrast comprising:

> a reaction-mixture tank for holding a reaction mixture containing DNA fragments and a reagent solution; . . .
> an <u>endless</u> recirculation-path system through which the reaction mixture in the reaction-mixture tank is fed and guided . . . the recirculation-path system therein being arranged *to circuit from and back to the reaction-mixture tank* . . .; and
> an intermittent-feed pump working to <u>circuit</u>-feed the reaction mixture unidirectionally through said recirculation-path.

(Emphasis added.)

Accordingly, recirculation according to the present invention requires a reaction-mixture tank, and a recirculation-path system that *circuits from and back to the reaction-mixture tank*.

In fact, cycling as taught in every one of the first five of the seven total embodiments described in Haff et al. is *reciprocation* as opposed to *recirculation*:

(1) <u>First embodiment</u>: Column 10, lines 44-53 in Haff et al. mention,

> The 4-way valve has a position in which reaction product from the length of tube 22 in the low temperature bath 18 can be pumped back into the high temperature bath 16 to commence a new cycle, a position for discharge of PCR products at the completion of a PCR protocol, and a position where new reaction mixture can be introduced to the reaction tube 22 after suitable procedures are performed to flush, clean or, if necessary, replace the reaction tube 22.

Clearly, this first-embodiment configuration of the technology taught by Haff et al. allows the reaction mixture to be reciprocated through the "continuous loop capillary thermal cycler" taught therein, but does not disclose, teach, or suggest a reaction-mixture tank, and a recirculation-path system that *circuits from and back to the reaction-mixture tank*, as recited in claim 4 of the present application.

Nor, it should be additionallfy noted, does Haff et al. disclose, teach, or suggest "an intermittent-feed pump working to <u>circuit</u>-feed the reaction mixture unidirectionally through [the] recirculation-path system," as recited in claim 4 of the present application.

(2) <u>Second embodiment</u>: Reciprocation of the reaction mixture according to the second embodiment of Haff et al. has been explained above.
(3) <u>Third embodiment</u>: The thermal cycler of the third embodiment in Haff et al. holds the reaction mixture in the capillary tube 62, and pumps in and flushes out water into the capillary-tube-containing chamber 60, to reciprocate the reaction mixture through different temperature cycles.

(4) <u>Fourth embodiment</u>: Here again, the reaction mixture sits while different temperature baths are flushed in and out of a chamber surrounding the mixture.

(5) <u>Fifth embodiment</u>: The reaction mixture is literally pumped back and forth—i.e., reciprocated—between metal-block heat exchangers at different temperatures.

(6) <u>Sixth embodiment</u>: No thermal cycling. The reaction mixture makes a single pass from cylinders 264 supplying syringes 262, into sample containers 244.

(7) <u>Seventh embodiment</u>: Ditto re the sixth embodiment. (The difference is that the heat exchanger blocks of sixth embodiment are replaced by a rotary cylindrical drum heat exchanger assembly.)

On page 5 of its August 28, 2006 communication, the Office states,

> It would have been *prima facie* obvious to a practitioner of ordinary skill in the art at the time of invention [to provide] a coiled heat-exchange section immersed into the reaction sections of Figure 1, since Haff suggests such a modification to control residence time of the reaction mixture in each temperature zone.

Yet Haff does not suggest coiling the reaction-mixture-containing capillary tube to control residence time, and as in the present invention, *to increase the amount of reaction mixture exposed to a given temperature bath at one time*.

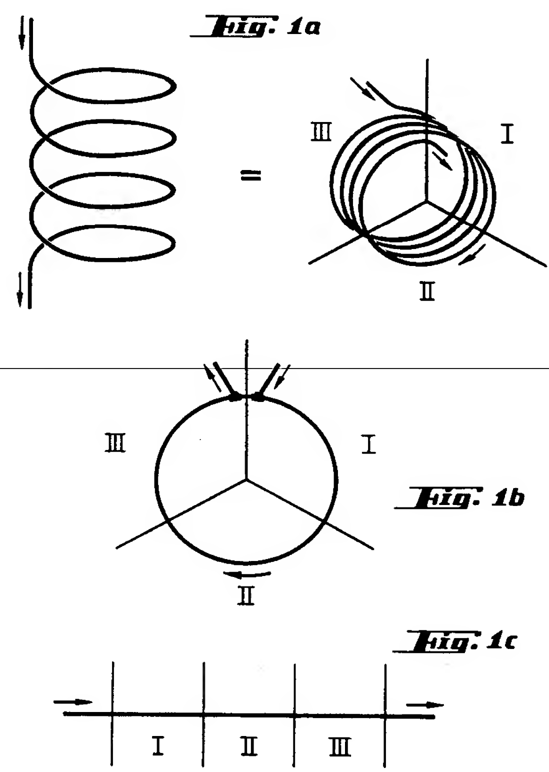
In fact, the Haff et al. teaching of zigzagging the reaction-mixture-containing tube is similar to the teaching by Larzul in U.S. Pat. No. 5,176,203, cited by Haff et al. in the background of their disclosure, and by the Office in the first action on the merits of the present application.

Column 3, lines 41-51 of Larzul state

> Various spatial arrangements of the capillary tube are envisaged. It may, for instance, be in a spiral form, in a closed loop form or in linear form. Each turn of the spiral, each turn of the closed loop or each passage of the length of linear capillary tube represents one thermal cycle, within which the sample passes through two or more thermostated zones, at different temperatures . . . . Further thermal cycles, up to 100, comprise the next turn of spiral, a further turn within the closed loop, or the return of the sample in reverse direction along the length of the linear capillary tube.

This capillary tube geometry is illustrated in FIG. 1a of Larzul. In the spiral form of FIG. 1a, there are as many loops as there are thermal cycles to be performed:

U.S. Patent Jan. 5, 1993 Sheet 1 of 3 5,176,203



Accordingly, the apparatuses of Haff et al., like the capillary tube geometries contemplated by Larzul *reciprocate* the reaction mixture, but do not *recirculate* it.

Page 5 of the August 28, 2006 Office action further states, "[A] practitioner of ordinary skill in the art would have recognized that the apparatus disclosed by Haff et al. could have been "scaled up" to produce larger amounts of amplification product."

The present invention, notwithstanding that scaling-up is may be a motivation behind it, is not scaling-up in and of itself.

The present invention as recited in claim 4 of the present application is an apparatus for continuous amplification of DNA, comprising:

> a reaction-mixture tank for holding a reaction mixture containing DNA fragments and a reagent solution; . . .
> an <u>endless</u> recirculation-path system through which the reaction mixture in the reaction-mixture tank is fed and guided . . . the recirculation-path system therein being arranged *to circuit from and back to the reaction-mixture tank* . . .; and
> an intermittent-feed pump working to <u>circuit</u>-feed the reaction mixture unidirectionally through said recirculation-path.

The invention as a result is able to perform large-volume amplification of DNA, the difficulty of which, in fact, in column 2, lines 40-57, the Haff et al. reference notes:

> The PCR volume has been limited to a range of from about 10 microliters to 1.5 milliliters in conventional heat block or liquid bath heat exchanger PCR instrument designs where the reaction mixture has been stored in microcentrifuge tubes. It is hard to scale up these volumes. The difficulty resides in the fixed dimensions of the wells in the heat exchange block for the tubes and the escalating difficulty in achieving heat transfer uniformity among all wells as dimensions get larger and heat gradient problems become more pronounced. As the volume of prior art reaction vessels is increased, the surface/volume ratio decreases. This change reduces the ability to change quickly the temperature of the reaction mixture in each tube because most heat exchange occurs between the walls of the tubes and the walls of the wells in the sample block.

It is respectfully submitted that the present invention, for reasons discussed in the foregoing, is a solution to the problems elaborated by Haff et al. in the above-quoted passage, yet a solution contradistinctive to the Haff et al. solution.

In response to Applicant's arguments in reply to the previous Office action, the Office states, "Haff teaches and/or suggest every element of the claimed invention," and therefore that the synergistic effect of the combination of elements that Applicant asserts is unique must be *prima facie* obvious. For the reasons presented above, it is respectfully submitted that Haff et al. fails to teach the unique combination of elements as now clearly set forth in claim 4, beginning with the very first element recited—the reaction-mixture tank.

The present invention shares some features of the Haff et al. and Larzul apparatuses, but in its unique combination of features, solves the technical problem of having to pass a given volume of reaction mixture in a single pass through the system. That is, the present invention recirculates the reaction mixture through paths whose length is determined not only by the time required by the denaturing, annealing, and elongation reactions, but by the recirculation itself. The just-noted technical problem is solved in the present invention, in other words, by the fact that the recirculation itself serves to control the volume of reaction mixture.

Since claim 4 is thus believed to be allowable over the prior art of record, it is respectfully submitted that the other pending claims, claims 6, 7 and 9-12 also rejected under this section, should also be held allowable as depending directly or indirectly from claim 4.

Accordingly, Applicant courteously urges that this application is in condition for allowance. Reconsideration and withdrawal of the rejections is requested. Favorable action by the Examiner at an early date is solicited.

Respectfully submitted,

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